Cyclin D1 promotes neurogenesis in the developing spinal cord in a cell cycle-independent manner.

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Public Summary:
In recent years, stem cell research has held a great deal of hope for regenerative medicine. The basic idea is to either stimulate endogenous stem cells or taking advantage of the recent isolation of human embryonic stem cells, which are capable of differentiating into any cell type. Reaching a successful outcome is dependent upon the development of protocols that efficiently and safely direct stem cell differentiation toward the desired cell type. As an example, intensive studies have been undertaken to produce motor neurons, which degeneration is encountered in Amyotrophic Lateral Sclerosis (ALS), a neurological disease characterized in the lost of voluntary muscle control. But to achieve this goal, there is a dire need for a better comprehension of the molecular mechanisms that control neuronal specification. Studies of embryonic development have helped tremendously. Although transcription factors that regulate the acquisition of neuronal phenotype have been identified, many studies have also pointed at the importance of the coordinated control of proliferation and differentiation. We thus investigated the molecular substrate that could explain the coordination of those two cellular processes. Interestingly, we found that Cyclin D1, a well-known key positive regulator of the cell cycle, unexpectedly regulates neuronal specification. Its over-expression in the chick spinal cord significantly increases neuronal production, without preventing terminal differentiation, whereas its down-regulation compromises it. Such role of Cyclin D1 in neuronal specification is not shared by other Cyclin Ds and is independent on its action on the cell cycle. Its molecular action would indeed involve the regulation of Notch pathway. Most importantly, this function is potent enough to convert Cyclin D2-expressing glial-restricted precursors into neurons. This is the first demonstration of a direct role of a cell cycle regulator in cellular specification. This could be used to promote neurogenesis in regions of the brain that have lost this capacity.

Scientific Abstract:
Neural stem and progenitor cells undergo an important transition from proliferation to differentiation in the G1 phase of the cell cycle. The mechanisms coordinating this transition are incompletely understood. Cyclin D proteins promote proliferation in G1 and typically are down-regulated before differentiation. Here we show that motoneuron progenitors in the embryonic spinal cord persistently express Cyclin D1 during the initial phase of differentiation, while down-regulating Cyclin D2. Loss-of-function and gain-of-function experiments indicate that Cyclin D1 (but not D2) promotes neurogenesis in vivo, a role that can be dissociated from its cell cycle function. Moreover, reexpression of Cyclin D1 can restore neurogenic capacity to D2-expressing glial-restricted progenitors. The neurogenic function of Cyclin D1 appears to be mediated, directly or indirectly, by Hes6, a proneurogenic basic helic-loop-helix transcription factor. These data identify a cell cycle-independent function for Cyclin D1 in promoting neuronal differentiation, along with a potential genetic pathway through which this function is exerted.

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